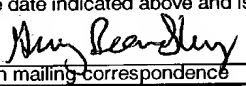


518 Rec'd PCT/PTO 02 AUG 2001

Certificate of Mailing		
Date of Deposit <u>August 2, 2001</u>	Label Number: <u>EL714747724US</u>	
I hereby certify under 37 C.F.R. § 1.10 that this correspondence is being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" with sufficient postage on the date indicated above and is addressed to BOX PCT, Assistant Commissioner for Patents, Washington, D.C. 20231.		
Printed name of person mailing correspondence <u>Guy Beardsley</u>	Signature of person mailing correspondence 	
Substitute Form PTO 1390 U.S. Department of Commerce Patent and Trademark Office TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		Attorney's Docket Number: 50125/026001 U.S. Application Number:
INTERNATIONAL APPLICATION NUMBER	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/00506	24.01.00	05.02.99
TITLE OF INVENTION:	cDNA SEQUENCE OF AN INTERACTOR FANCIP1 OF THE FANCONI ANAEMIA PROTEIN OF COMPLEMENTATION GROUP A	
APPLICANTS FOR DO/EO/US:	Hans Gross et al.	
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1.	<input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. § 371.	
2.	<input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. § 371.	
3.	<input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. § 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. § 371(b) and PCT Articles 22 and 39(1).	
4.	<input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19 th month from the earliest claimed priority date.	
5.	<input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. § 371(c)(2)). <input type="checkbox"/> a. is transmitted herewith (required only if not transmitted by the International Bureau). <input checked="" type="checkbox"/> b. has been transmitted by the International Bureau. <input type="checkbox"/> c. is not required, as the application was filed with the United States Receiving Office (RO/US).	
6.	<input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. § 371(c)(2)).	
7.	<input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. § 371(c)(3)). <input type="checkbox"/> a. are transmitted herewith (required only if not transmitted by the International Bureau). <input type="checkbox"/> b. have been transmitted by the International Bureau. <input type="checkbox"/> c. have not been made; however, the time limit for making such amendments has NOT expired. <input checked="" type="checkbox"/> d. have not been made and will not be made.	
8.	<input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. § 371(c)(3)).	
9.	<input checked="" type="checkbox"/> An oath or declaration of the inventors (35 U.S.C. § 371(c)(4)). (Unsigned)	
10.	<input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. § 371(c)(5)).	
11.	<input type="checkbox"/> An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98.	
12.	<input type="checkbox"/> An assignment for recording. A separate cover sheet in compliance with 37 §§ 3.28 and 3.31 is included.	
13.	<input checked="" type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.	
14.	<input type="checkbox"/> A substitute specification.	
15.	<input type="checkbox"/> A change of power of attorney and/or address letter.	
16.	<input checked="" type="checkbox"/> Other items or information: PCT/RO/101 form, PCT/ISA/210 form, PCT/IPEA/416 form, PCT/IPEA/409 form and PCT/IB/306 form	

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JC05 Rec'd PCT/PTO 0 2 AUG 2001

17.	<p>■ The following fees are submitted: BASIC NATIONAL FEE (37 C.F.R. § 1.492(A)(1)-(5)):</p> <p>Neither international preliminary examination fee (37 C.F.R. § 1.482) nor international search fee (37 C.F.R. § 1.455(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$ 1000.00</p> <p>International preliminary examination fee (37 C.F.R. § 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$ 860.00</p> <p>International preliminary examination fee (37 C.F.R. § 1.482) not paid to USPTO but international search fee (37 C.F.R. § 1.445(a)(2)) paid to USPTO \$ 710.00</p> <p>International preliminary examination fee (37 C.F.R. § 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1) - (4) \$ 690.00</p> <p>International preliminary examination fee paid to USPTO (37 C.F.R. § 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$ 100.00</p>			\$860.00
ENTER APPROPRIATE BASIC FEE AMOUNT =			\$860.00	
Surcharge of \$130 for furnishing the oath or declaration later than <input type="checkbox"/> 20 OR <input type="checkbox"/> 30 months from the earliest claimed priority date (37 C.F.R. § 1.492(e)).			\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	60 - 20 =	0	x \$18	
Independent claims	1 - 3 =	0	x \$80	
Multiple dependent claims (if applicable)			+ \$270	
TOTAL OF ABOVE CALCULATIONS =			\$1850.00	
SMALL ENTITY STATUS:				
Applicant claims small entity status under 37 CFR 1.27.				
Reduction of 1/2 for filing by small entity, if applicable Applicant claims small entity status under 37 C.F.R. § 1.27			\$ 925.00	
SUBTOTAL =			\$925.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 OR <input type="checkbox"/> 30 months from the earliest claimed priority date (37 C.F.R. § 1.492(f)).			+	
TOTAL NATIONAL FEE =			\$925.00	
Fee for recording the enclosed assignment (37 C.F.R. 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§ 3.28, 3.31). \$40.00 per property.			+	
TOTAL FEES ENCLOSED =			\$ 925.00	
			Amount to be refunded	
			\$	
			charged	
			\$	
<p>■ a. A check in the amount of \$925.00 to cover the above fees is enclosed.</p> <p><input type="checkbox"/> b. Please charge my Deposit Account No. 03-2095 in the amount of \$ [***] to cover the above fees.</p> <p>■ c. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 03-2095.</p>				
NOTE: Where an appropriate time limit under 37 C.F.R. §§ 1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. § 1.137(a) or (b) must be filed and granted to restore the application to pending status.				
<p>SEND ALL CORRESPONDENCE TO:</p> <p>Karen L. Elbing, Ph.D. Clark & Elbing LLP 176 Federal Street Boston, MA 02110-2214 Telephone: 617-428-0200 Facsimile: 617-428-7045</p>		<p>Signature Karen L. Elbing, Ph.D. Reg No. 35,238</p>		



21559

PATENT TRADEMARK OFFICE Revised: 17 March 2000

09890689 080201

09/890689

JC05 Rec'd PCT/PTO 02 AUG 2001

PATENT

ATTORNEY DOCKET NO. 50125/026001

Certificate of Mailing	
Date of Deposit <u>August 2, 2001</u>	Label Number: <u>EL714747724US</u>
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<u>Guy Beardsley</u> Printed name of person mailing correspondence	<u>Guy Beardsley</u> Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hans Gross et al.	Art Unit:	
Serial No.:	Not yet assigned	Examiner:	
Filed:	August 2, 2001	Customer No.:	21559
Title:	cDNA SEQUENCE OF AN INTERACTOR FANCIPI OF THE FANCONI ANAEMIA PROTEIN OF COMPLEMENTATION GROUP A		

Assistant Commissioner For Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Prior to examination, kindly amend the above-referenced application as follows.

In the claims:

Amend claims 1, 2, 4, 5, 7, 8, and 10-24 as follows.

1. Nucleic acid, which includes
 - a) the nucleotide sequence shown in Fig.1 or a protein-coding segment thereof,
 - b) one of the sequences from a) within the context of the degeneration of the genetic code corresponding to the nucleotide sequence,
 - c) a sequence that hybridizes under stringent conditions with one [with] of the sequences from a) and/or b) [under stringent conditions hybridizing nucleotide sequence], except for the EST sequences: AA165403, AA455594, AA314472, N34087, AA452340, AA182700, N41615, AA470049, AI751597, AA463289, AA132459, W31487, R56355,

H58271, H16122, W77956, AA193332, AA323923, AA370209, AA296758, W72757, AA093971, AA385544, AA386175, AA165402, AW085713, H42806, AA093977, AI161152, AA370011, AI671702, R71215, AA885343, T79297, AI814869, R81567, AI082713, N29615, AW087726, AW075710, AI952608, AI818073, AI784445, AI432812, AI375568, AI372904, AI364106, AI143379, AA993074, AA953985, AA862385, AA761084, AA576229, AA569223, AA463198, AA452117, AA416877, AA074872, W16851, W04568, N40176, AW068354, AA857004, H58663, H15819, AW264944, AI923965, AI692214, AI475321, AI435987, AA961068, AA206059, AI469161, T84789, AA507257, AA707515, AA132458, AA179262, T79211, W31505, N25699, T99574, T99363, AI751598, AA713668, T91119, AW105515, AA370208, AI422128, R81568, AI038899, AI971847, AI540650, AI826106, AA885960, R56263, AA825431, T99147, D31503 and AF049564, or

- d) a complementary sequence to the sequences of a) and/or b).
2. Nucleic acid according to claim 1, which includes a protein-coding segment comprising [of preferably] at least 30 nucleotides of the nucleotide sequence shown in Fig. 1.
 4. Modified nucleic acid or nucleic acid analogue, which includes a nucleotide sequence according to [one of the claims 1 to 3] claim 1.
 5. Recombinant vector, which includes at least one copy of a nucleic acid according to [one of the claims 1 to 3] claim 1 or a section thereof.
 7. A transformed cell, non-human transgenic organism, or animal model comprising [With] a nucleic acid according to [one of the claims 1 to 3] claim 1 or a vector according to claim 5 [or 6 transformed cell, a corresponding non-human transgenic organism or animal models], which stably produce (knock-in) the product of the nucleic acid according to [one of the claims 1 to 3] claim 1 or whose corresponding natural gene was destroyed deliberately (knock-out).

8. Polypeptide or a salt thereof, which is coded by a nucleic acid according to [one of the claims 1 to 3] claim 1.
10. Fragment of the polypeptide according to claim[s] 8 [or 9] with at least 100 amino acids or salts thereof.
11. Modified polypeptide, which includes an amino acid sequence according to claim[s] 8 [or 9].
12. Method[s] for the synthesis of the polypeptide according to claim 8 [or 9], which includes the cultivation of cells according to claim 7 [as well as] and the isolation of the polypeptide according to claim 8 [or 9].
13. A method for producing an antibody against the polypeptide of claim 8, comprising contacting an antibody-producing cell with [Use of] a polypeptide according to claim 8 [or 9] or [of] fragments of this polypeptide as an immunogen [for the production of antibodies].
14. Antibodies against a polypeptide according to claim 8 [or 9].
15. Method for the identification of effectors of a protein according to claim 8 [or 9], with the help of which various potential effector substances can be tested on cells, which express the protein.
16. Pharmaceutical composition, which includes as an active component
 - a) a nucleic acid according to [one of the claims 1 to 4] claim 1,
 - b) a vector according to claim 5 [or 6],
 - c) a cell according to claim 7,
 - d) a polypeptide according to claim 8, [9,]10 or 11,
 - e) an antibody according to claim 14

and which contains the pharmaceutically usual carrier, auxiliary and/or additive substances.

17. A method of diagnosing a disease [Use of a composition according to claim 16 for diagnosis of diseases,] which [are] is associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression, or a predisposition to such a disease[s] comprising the use of a composition according to claim 16.

18. A method of diagnosing a disease [Use of a pharmaceutical composition for diagnosis of diseases] which [are] is associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression, or a predisposition to such a disease[s], comprising the use of a composition which contains as an active component
 - a) an EST sequence according to claim 1c,
 - b) a recombinant vector which includes at least one copy of the EST sequences mentioned above,
 - c) a recombinant vector according to b) which enables the expression of the nucleic acid in a suitable host cell,
 - d) a cell according to claim 7, whereas the nucleic acid consists of one of the EST sequences mentioned above,
 - e) a polypeptide being coded by one of the EST sequences mentioned above or a salt thereof or,
 - f) a polypeptide according to e) which exhibits the amino acid sequence shown in Fig.2 or a homology of more than 60% with the amino acid sequence shown in Fig.2 or a salt thereof,
 - g) a fragment of the polypeptide according to e) or f) with at least 100 amino acids or a salt thereof,
 - h) a modified polypeptide which includes an amino acid sequence according to e) or f),
 - i) an antibody against a polypeptide according to e) or f)
 and which contains pharmaceutically usual carrier, auxiliary and/or additive substances.

19. A method for treating or preventing a disease [Use of a composition according to claim 16 for the therapy or prevention of diseases,] which [are] is associated with DNA repair

defects, cell cycle disorders, cytopenia, tumor genesis and/or tumor progression, comprising administering a composition of claim 16.

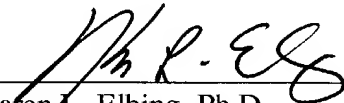
20. A method for treating or preventing a disease [Use of a pharmaceutical composition according to claim 18 for the therapy or prevention of diseases,] which [are] is associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression, comprising administering a composition of claim 18.
21. The method of claim 19, wherein said treating or preventing is carried out by [Use of a composition according to claim 16 for a] gene therapy [of diseases, which are associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression].
22. The method of claim 20, wherein said treating or preventing is carried out by [Use of a pharmaceutical composition according to claim 18] for gene therapy [of diseases which are associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression].
23. Method[s] for diagnosing diseases, which are associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression or a predisposition to such diseases, during which a patient or a sample from the patient is brought in contact with a composition according to claim 16 and the nucleotide sequence and/or the expression of a nucleic acid according to claim 1 is determined.
24. Method[s] for the therapy or prevention of diseases, which are associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression, during which a patient is administered a composition according to claim 16, which contains the active components in an amount effective against the disease.

If there are any other charges, or any credits, please apply them to Deposit Account No.

03-2095.

Respectfully submitted,

Date: 2 August 2001



Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
176 Federal Street
Boston, MA 02110-2214
Telephone: 617-428-0200
Facsimile: 617-428-7045

50125.026001 Preliminary Amendment



21559

PATENT TRADEMARK OFFICE



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PATENT
ATTORNEY DOCKET NUMBER: 50125/026001Certificate of Mailing: Date of Deposit: November 19, 2001

I hereby certify under 37 C.F.R. § 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Colleen Coyne

Printed name of person mailing correspondence

Colleen Coyne

Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hans Joachim Gross et al.

Art Unit:

Serial No.: 09/890,689

Examiner:

Filed: August 2, 2001

Customer No.: 21559

Title: cDNA SEQUENCE OF AN INTERACTOR FANCIPI OF THE
FANCONI ANAEMIA PROTEIN OF COMPLEMENTATION GROUP
A

Assistant Commissioner for Patents
Washington, D.C. 20231

SEQUENCE AMENDMENT

In reply to the Notice to Comply mailed September 17, 2001, kindly amend the
above-referenced specification as follows.

Replace page 9, first paragraph (lines 1-8) with the following amended paragraph
rewritten in clean form:

Sequence analysis of the FANCIPI cDNA

The length of the gene bank cDNAs of the isolated interactor clones has been determined through EcoRI/XhoI restriction hydrolysis. The initial sequencing of the cDNAs took place through an automated cycle sequencing method (Applied Biosystems) using the nucleic acid primer Bco I (5' - ACC AGC CTC TTG CTG AGT GGA GAT G-3') (SEQ ID NO: 3). The complete sequencing of the vector with inserted FANCIPI cDNA fragment occurred with the nucleic acid primers BcoI and BcoII (5' - GAC AAG CCG

ACA ACC TTG ATT GGA G-3') (SEQ ID NO: 4) done by the company Sequence Laboratories Göttingen.

Replace page 9, second paragraph (lines 10-21) with the following amended paragraph rewritten in clean form:

For determination of the 5' part sequence of the foand nucleotide sequence the 5'/3'RACE Kit (Boehringer Roche) has been used. The following sequence specific primers have been used: FANCIP1-SP1 (5' -GGG GGC AGG AAT ATG AGA GG-3') (SEQ ID NO: 5) and FANCIP1-SP2 (5' -TTT AGG GGG AAG TGT ACC TG-3') (SEQ ID NO: 6). The received PCR product has been cleaned electrophoretically (JETquick Gel Extraction Kit, GENOMED) and directly sequenced using the T7 Sequenase Version 2.0 DNA Sequence Kit (Amersham-Pharmacia) and the primer FANCIP1-SP2 as named above. The belonging of the obtained nucleotide fragment to the plasmid-inserted interactor fragment has been verified through an overlapping sequence area of 38 nucleotides. The assembled nucleotide sequence delivered a cDNA area being 1553 nucleotides long including a part of the 5' untranslated region, the whole open reading frame of 924 nucleotides and 308 codons respectively and the almost complete 3' untranslated region up to the polyadenylation signal (AATAAA) (SEQ ID NO: 7).

Insert the Sequence Listing submitted herewith at the end of the application.

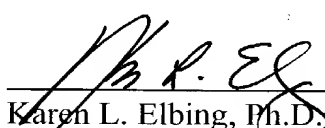
REMARKS

No new matter has been added by these amendments.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 19 November 2001


Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
176 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045



VERSION WITH MARKINGS TO SHOW CHANGESIn the Specification:

A marked up version of page 9, first paragraph (lines 1-8), up to line 31, of the specification is presented below.

Sequence analysis of the FANCIP1 cDNA

The length of the gene bank cDNAs of the isolated interactor clones has been determined through EcoRI/XhoI restriction hydrolysis. The initial sequencing of the cDNAs took place through an automated cycle sequencing method (Applied Biosystems) using the nucleic acid primer Bco I (5' - ACC AGC CTC TTG CTG AGT GGA GAT G-3') (SEQ ID NO: 3). The complete sequencing of the vector with inserted FANCIP1 cDNA fragment occurred with the nucleic acid primers BcoI and BcoII (5' - GAC AAG CCG ACA ACC TTG ATT GGA G-3') (SEQ ID NO: 4) done by the company Sequence Laboratories Göttingen.

A marked up version of page 9, second paragraph (lines 10-21), of the specification is presented below.

For determination of the 5' part sequence of the foand nucleotide sequence the 5'/3'RACE Kit (Boehringer Roche) has been used. The following sequence specific primers have been used: FANCIP1-SP1 (5' -GGG GGC AGG AAT ATG AGA GG-3') (SEQ ID NO: 5) and FANCIP1-SP2 (5' -TTT AGG GGG AAG TGT ACC TG-3') (SEQ ID NO: 6). The received PCR product has been cleaned electrophoretically (JETquick Gel Extraction Kit, GENOMED) and directly sequenced using the T7 Sequenase Version 2.0 DNA Sequence Kit (Amersham-Pharmacia) and the primer FANCIP1-SP2 as named above. The belonging of the obtained nucleotide fragment to the plasmid-inserted interactor fragment has been verified through an overlapping sequence area of 38 nucleotides. The assembled nucleotide sequence delivered a cDNA area being 1553 nucleotides long including a part of the 5' untranslated region, the whole open reading frame of 924 nucleotides and 308 codons respectively and the almost complete 3' untranslated region up to the polyadenylation signal (AATAAA) (SEQ ID NO: 7).

SEQUENCE LISTING

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 Shmidt, Werner
 Reuter, Tanja
 Hoehn, Holger
 Heterich, Sabine

<120> cDNA Sequence of an Interactor FANCIP1
 of the Fanconi Anaemia Protein of Complementation Group A

<130> 50125/026001

<140> US 09/890,689

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Anm. 99/001 WO

cDNA sequence of an interactor FANCIP1 of the Fanconi anaemia protein of
complementation group A

Description

Field of the invention

- 10 The present invention relates to the cDNA of an interactor FANCIP1 of the Fanconi
anaemia protein of the complementation group A (FANCA) as well as the thereof coded
protein. Further issues are the corresponding gene, antibodies against the protein,
FANCIP1-transgenic organisms and cells as well as the use of FANCIP1 for effector
screening and the pharmaceutical application of the nucleic acid, the proteins and the
15 antibodies.

Background of the invention

- Fanconi anaemia (further being called FA) is an autosomal recessive inheritable disease
manifested by clinical symptoms such as progressive pancytopenia, congenital
20 malformations and higher risk of cancer (Glanz and Fraser, 1982). At least 15% of FA-
patients develop myeloid leukaemia (Auerbach and Allen, 1991).

- Cytogenetically FA cells are characterized by a hypersensitivity to DNA cross-linking
agents, e.g. mitomycin C (MMC) and diepoxybutane (DEB), manifested by chromosomal
25 breaks and aberrations (Auerbach, 1993). After treatment with MMC FA lymphoblasts and
fibroblasts show a retardation or an arrest in the G2-phase of the cell cycle (Kubbies et al.,
1985; Seyschab et al., 1995). Additionally, a higher oxygen-sensitivity of FA cells has
been reported (Joenje et al., 1981; Schindler and Hoehn, 1988; Poot et al., 1996).

- 30 On the basis of somatic cell fusion studies at least eight different complementation groups
(A to H) could be distinguished for FA (Joenje et al., 1997). Up to now genes for three
complementation groups could be identified: FANCC (Strathdee et al., 1992;
WO93/22435), FANCA (Lo Ten Foe et al., 1996; The Fanconi anaemia/Breast cancer
consortium, 1996; WO98/14462) and FANCG (Saar et al., 1998; De Winter et al., 1998).

Although the molecular functioning of the FA proteins is still unknown the cellular phenotype and the higher risk of cancer through a defect gene indicate a participation in DNA repair, cell cycle regulation and/or haematopoiesis. The similarity of the clinical and cellular phenotype of the different complementation groups and the findings that the FANCA and FANCC protein interact through FANCA phosphorylation and being transported into the cell nucleus as a complex (Kupfer et al., 1997a, Yamashita et al., 1998) point to a protein cascade or a functional co-effect in a complex. The participation in this complex could also be shown for FANCG (Garcia-Higuera et al., 1999; Waisfisz et al., 1999; Reuter et al., 2000).

10

Crucial progress with revealing the molecular cause for the FA pathogenesis can be obtained through the identification of the participating genes and proteins. The following FANCC interactors are published up to now: cyclin-dependent kinase cdc2 (Kupfer et al., 1997b), the chaperone GRP94 (Hoshino et al., 1998), the NADPH-cytochrome P450 reductase (Kruyt et al., 1998) and a new transcription repressor (Hoatlin et al., 1999), as FANCA interactor the nexin SNX5 (Otsuki et al., 1999), as FANCA and FANCC interactor alpha spectrin II (McMahon et al., 1999). Fanconi gene 1 and 2 have been classified as potentially relevant for the pathogenesis (Planitzer et al., 1998; WO98/16637 and WO98/45428).

20

It was the object of the present invention to find interactors of the Fanconi anaemia proteins FANCA and FANCC. Based upon the FA pathogenesis as a model system for mechanisms maintaining the genetic stability the goal was to identify parts of a protein complex or a protein cascade which play a role in DNA repair, cell cycle regulation and/or oncogenesis.

25

Summary of the invention

The present invention describes the identification of a cDNA which codes for a new protein termed FANCIP1 (Fanconi anaemia protein interacting protein 1). The cDNA sequence has been found using an interaction trap version of the yeast two-hybrid system (Fields and Song, 1989; Finley Jr. et al., 1996) whereas the protein of the complementation group A (FANCA) has been used as bait. The protein being coded through the FANCIP1 cDNA interacts with FANCA and thus can be part of the complex or the signal

30

transduction cascade which leads to FA pathogenesis if defect. The FANCIPI cDNA and the encoded protein as much as the corresponding gene and antibodies against the protein are useful as diagnostic, therapeutic or preventive tools for diseases being associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor
 5 progression. Furthermore, they can serve as targets for effector screening processes to develop new drugs for the treatment of diseases as mentioned before.

The present invention concerns one nucleic acid which contains

- 10 a) the nucleotide sequence or a protein-coding part of it shown in Fig.1
- b) one of the sequence from a) within the context of the degeneration of the genetic code corresponding nucleotide sequence
- c) one with the sequences from a) and/or b) under stringent conditions hybridizing nucleotide sequence or
- 15 d) one to a sequence from a) and/or b) complementary sequence

The nucleotide sequence being shown in Fig.1 contains an open reading frame which corresponds to a protein with a length of 308 amino acids. The amino acid sequence of this protein is shown in Fig.2.

- 20 In the EST data base of the National Center for Biotechnology Information (NCBI) human cDNA clones can be found which contain parts of the nucleotide sequence shown in Fig.1. The following human ESTs are mentioned:

Access-numbers AA165403, AA455594, AA314472, N34087, AA452340, AA182700, N41615, AA470049, AI751597, AA463289, AA132459, W31487, R56355, H58271,
 25 H16122, W77956, AA193332, AA323923, AA370209, AA296758, W72757, AA093971, AA385544, AA386175, AA165402, AW085713, H42806, AA093977, AI161152, AA370011, AI671702, R71215, AA885343, T79297, AI814869, R81567, AI082713, N29615, AW087726, AW075710, AI952608, AI818073, AI784445, AI432812, AI375568, AI372904, AI364106, AI143379, AA993074, AA953985, AA862385, AA761084,
 30 AA576229, AA569223, AA463198, AA452117, AA416877, AA074872, W16851, W04568, N40176, AW068354, AA857004, H58663, H15819, AW264944, AI923965, AI692214, AI475321, AI435987, AA961068, AA206059, AI469161, T84789, AA507257, AA707515, AA132458, AA179262, T79211, W31505, N25699, T99574, T99363, AI751598, AA713668, T91119, AW105515, AA370208, AI422128, R81568, AI038899,

AI971847, AI540650, AI826106, AA885960, R56263, AA825431, T99147, D31503 and AF049564. Among these numbers no information about a complete open reading frame or a possible biological function is given.

- 5 The search for functional domains of the FANCIP1 protein (Fig.2) using the ProfileScan Server of the ISREC Bioinformatics Group (Swiss Institute for Experimental Cancer Research) provided as the most significant result an esterase/lipase/thioesterase domain.

Besides the nucleotide sequence shown in Fig.1 and a nucleotide sequence corresponding
10 to that sequence within the context of the degeneration of the genetic code the present invention comprises another nucleotide sequence which hybridizes with one of the sequences mentioned before. The term hybridization according to the present invention is being used as in Sambrook et al. (1989).

- 15 The nucleic acid of the present invention encloses a protein-coding part of the nucleotide sequence being shown in Fig.1 or a sequence showing a homology of more than 65% preferably more than 80% or showing a part of the sequence of preferably at least 15 nucleotids. In addition the nucleotide sequence may enclose an RNA or an analogue of the nucleic acid, e.g. a peptide-nucleic acid.

20 The nucleic acids of the present invention can be isolated from mammals according to known techniques using short parts of the nucleotide sequence as shown in Fig.1 as hybridization probes and/or as primer according to known methods. Nucleic acids can be furthermore produced by chemical synthesis where modified nucleotide components (e.g.
25 methylized or 2'-O-alkylized nucleotides or phosphorthioates) can be used instead of the usual nucleotide elements. Nucleic acids consisting partly or wholly of modified nucleotide components can be used for example as a therapeutic drug such as antisense nucleic acids or ribozymes.

- 30 The present invention concerns furthermore a vector which contains at least one copy of a nucleic acid of the present invention. This vector can be any prokaryotic or eukaryotic vector containing the nucleic acid of the present invention and/or making the expression of the nucleic acid of the present invention in a suitable host cell possible. Examples for prokaryotic vectors are chromosomal vectors such as bacteriophages and

extrachromosomal vectors such as circular plasmid vectors. Examples for eukaryotic vectors are yeast vectors or vectors being suitable for higher cells such as plasmid vectors or viral vectors.

- 5 The invention also concerns a vector which preferably contains a part of at least 15 nucleotides of the sequence shown in Fig.1. Preferably this part contains a nucleotide sequence being derived from the protein-coding area of the sequence being shown in Fig.1 or from an area important for the expression of the protein. These nucleic acids are especially suitable for the production of therapeutic applicable antisense-nucleic acids.

10

The present invention concerns furthermore a cell being transformed with a nucleic acid or a vector, both of the present invention. The cell can as well be a prokaryotic as an eukaryotic cell. Examples for eukaryotic cells are mammalian cells in particular. Further objects are FANCIP1-transgenic organisms such as knock-in or knock-out animal models.

- 15 Animal models stably expressing the product of the nucleic acid are being called knock-in animal models, those whose corresponding gene has been destroyed are being called knock-out animal models.

- The present invention includes a protein coded by a sequence as mentioned above. This
20 protein contains the amino acid sequence as shown in Fig.2 or a homology of more than 60% preferably more than 70% to the amino acid sequence shown in Fig.2. The invention also concerns variations and fragments of the protein being shown in Fig.2. Variations are sequences which differ from the amino acid sequence shown in Fig.2 by substitution, deletion and/or insertion of individual amino acids or short amino acid chains. Among
25 these are naturally existing allelic variations or splicevariations of FANCIP1 as well as proteins produced by means of recombinant DNA technology, especially proteins obtained through in vitro-mutagenesis using chemically synthesized oligonucleotides which regarding their biological and/or immunological activity mostly respond to the protein shown in Fig.2. This definition also includes chemically modified polypeptides. Among
30 these are polypeptides having been modified at the termini and/or at reactive amino acid side groups through acylation or amidation.

The invention also concerns procedures leading to the production of the protein of the present invention including the cultivation of transformed cells as much as the isolation of the protein of the present invention.

- 5 Furthermore, the invention concerns the use of the polypeptide of the present invention or fragments of this polypeptide as immunogen for the production of antibodies. The production of antibodies can take place by usual means of immunizing experimental animals with the complete polypeptide or fragments thereof followed by obtaining the resultant polyclonal antiserum. Monoclonal antibodies can be produced using known
10 methods. The present invention covers antibodies against FANCIP1 or a variation of it, too.

- FANCIP1 encoded by the nucleic acid of the present invention can be used as a target for a specific search for effectors. Substances having an inhibitory or activating effect on the
15 protein of the present invention are able to influence selectively the cell functions being usually regulated by the protein itself. Therefore they can be used for the therapy of appropriate clinical pictures, e.g. cytopenia or tumors. A part of the invention is also a method for identification of effectors of FANCIP1 where cells expressing the protein are being brought into contact with different potential effector substances and the cells are
20 being analysed in regard of changes, e.g. cell activating, cell inhibiting, cell proliferation and/or cell genetic changes. By this means binding domains of FANCIP1 can be identified. Part of the invention are pharmaceutically effective effector-substances which are gained by the method described above.

- 25 The present invention also concerns a pharmaceutical composition containing nucleic acids, vectors, cells, polypeptides, antibodies and/or effector-substances as described earlier as active components and also may carry usual pharmaceutical carrier, auxiliary and/or additive substances as much as other active components. The pharmaceutical composition can be used specifically for diagnosis, therapy or prevention of diseases being associated
30 with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression. This is also valid for the diagnosis of a predisposition for such diseases in individuals especially for the diagnosis of a risk of cytopenia and/or tumor diseases. Furthermore a focused diagnosis of diseases being connected with direct or indirect changes of the activity of FANCIP1 is made possible. Using specific nucleic acid probes

these examinations can be accomplished at the nucleic acid level, e.g. at gene or transcription level, or with the help of antibodies against FANCIPI1 at the protein level.

With clinical pictures being traced back to a breakdown of FANCIPI1 a gene therapeutical
5 treatment can follow which includes the transmission of a nucleic acid encoding FANCIPI1
via vectors, e.g. viral vectors, into the corresponding final tissue. On the other side a
genetherapeutical treatment can take place on clinical pictures tracing back to an
uncontrolled expression of FANCIPI1 which leads to the blockade of this expression.

- 10 The present invention also includes a method for the diagnosis of the diseases mentioned
above where contact between a patient or a sample from the patient, e.g. a sample of a
body liquid or of a tissue, and a pharmaceutical composition of the invention is established
and where the nucleotide sequence and/or the expression of the nucleic acid of the
invention is determined qualitatively or quantitatively. These methods of determination can
15 take place at the level of nucleic acids by using nucleic acid hybridization probes or
through reverse transcription/PCR and at the protein level by using antibodies in cyto- or
histochemical methods respectively. The pharmaceutical composition can be used as a
marker for the appearance of cytopenias, tumors or other diseases being connected with
proliferation or a predisposition for the named pathophysiological changes.

- 20 Finally, the present invention includes a procedure for a therapy or prevention of one of the
diseases mentioned above where the patient is given a pharmaceutical composition of the
present invention including the active component in an effective amount for the disease.
Specific examples for pharmaceutical compositions being suitable for therapeutic use are
25 amongst others bispecific antibodies and antibody-toxins and antibody-enzyme conjugates
respectively. Other favoured pharmaceutical compositions for therapeutical use are
antisense nucleic acids, gene therapy vectors or effector substances, e.g. in form of low
molecular activators or inhibitors.

30 Detailed description of the invention

Interaction trap

For the cloning of cDNAs whose gene products interact with the Fanconi anaemia protein
FANCA and therefore may play a role in the FA pathogenesis an interaction trap version
of the yeast two-hybrid system has been used.

With pEG202FANCA and the B42-fusion-cDNA-bank co-transformed EGY48 have been preselected based on the existence of both vectors on leucine-containing medium and have been taken up. For the search of interacting yeast clones aliquots have been spread on leucine-free medium and incubated 3 to 5 days at 30°C. Altogether aliquots according to an amount of 1×10^6 transfectants have been screened. The dependence of the transcriptional activation of positive clones upon the expression of the prey protein has been tested on leucine-free medium. The isolation of the interactor plasmids has been carried out by growing yeasts in glucose-medium without tryptophane, electroporation of the nucleic acid isolate in the E.coli strain XL1blue (Stratagene) and plasmid preparation of bacteria cells. For confirmation of the interactions retransformations of the isolated prey interactor, in combination with different bait structures, have been carried out. The observed interaction has been verified in combination with pEG202FANCA. In addition possible interactions with the LexA fusion partner could be excluded by co-retransformation with the pEG202 empty vector on the one hand and with a LexA-DNA-ligase-bait fusion construct as a negative control on the other hand.

Sequence analysis of the FANCIP1 cDNA

The length of the gene bank cDNAs of the isolated interactor clones has been determined through EcoRI/XhoI restriction hydrolysis. The initial sequencing of the cDNAs took place through an automated cycle sequencing method (Applied Biosystems) using the nucleic acid primer Bco I (5'- ACC AGC CTC TTG CTG AGT GGA GAT G-3'). The complete
 5 sequencing of the vector with inserted FANCIP1 cDNA fragment occurred with the nucleic acid primers BcoI and BcoII (5'- GAC AAG CCG ACA ACC TTG ATT GGA G-3') done by the company Sequence Laboratories Göttingen.

- 10 For determination of the 5' part sequence of the found nucleotide sequence the 5' / 3' RACE Kit (Boehringer Roche) has been used. The following sequence specific primers have been used: FANCIP1-SP1 (5'-GGG GGC AGG AAT ATG AGA GG-3') and FANCIP1-SP2 (5'-TTT AGG GGG AAG TGT ACC TG-3'). The received PCR product has been cleaned electrophoretically (JETquick Gel Extraction Kit, GENOMED) and directly sequenced
 15 using the T7 Sequenase Version 2.0 DNA Sequencing Kit (Amersham-Pharmacia) and the primer FANCIP1-SP2 as named above. The belonging of the obtained nucleotide fragment to the plasmid-inserted interactor fragment has been verified through an overlapping sequence area of 38 nucleotides. The assembled nucleotide sequence delivered a cDNA area being 1553 nucleotides long including a part of the 5' untranslated region, the whole
 20 open reading frame of 924 nucleotides and 308 codons respectively and the almost complete 3' untranslated region up to the polyadenylation signal (AATAAA).

- In order to find similar nucleotide sequences in the sequence data base of the National Center of Biotechnology Information (NCBI) the cDNA sequence of FANCIP1 (Fig. 1)
 25 has been analysed using the Blast program at the NCBI (<http://www.ncbi.nlm.nih.gov/cgi-bin/BLAST/nph-newblast?Jform=1>). Significant homologies to human clones only occurred in the EST database but neither included a complete open reading frame nor information to a possible biological function.

- 30 For the determination of potentially functional domains within the FANCIP1 protein the amino acid sequence (Fig. 2) has been analysed using the ProfileScan server of the ISREC Bioinformatics Group (http://www.isrec.isb-sib.ch/software/PFSCAN_form.html).

Short description of the figures

Fig.1 (SEQ ID NO.1) a nucleotide sequence including the open reading frame encoding FANCIP1,

5

Fig.2 (SEQ ID NO.2) the amino acid sequence of an open reading frame of the nucleotide sequence shown in Figure 1,

Fig.3 (SEQ ID NOs. 3 and 4) the nucleic acid primer used for the sequencing of the plasmid-inserted FANCIP1 nucleotide sequence,

10

Fig.4 (SEQ ID NOs. 5 and 6) the nucleic acid primer used for the 5' RACE analysis.

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WO 00/46244

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PCT/EP00/00506

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 35 40 45
 20 Leu Pro Pro Val Ser Gly Thr Ala Asp Val Phe Phe Arg Gln Ile Leu
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 Ala Leu Thr Gly Trp Gly Tyr Arg Val Ile Ala Leu Gln Tyr Pro Val
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 85 90 95
 30 His Leu Gln Leu Asp Lys Val His Leu Phe Gly Ala Ser Leu Gly Gly
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 Phe Leu Ala Gln Lys Phe Ala Glu Tyr Thr His Lys Ser Pro Arg Val
 115 120 125
 35 His Ser Leu Ile Leu Cys Asn Ser Phe Ser Asp Thr Ser Ile Phe Asn
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 Gln Thr Trp Thr Ala Asn Ser Phe Trp Leu Met Pro Ala Phe Met Leu
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 40 Lys Lys Ile Val Leu Gly Asn Phe Ser Ser Gly Pro Val Asp Pro Met ,
 165 170 175
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 Gln Ser Glu Leu Ala Ser Arg Leu Thr Leu Asn Cys Gln Asn Ser Tyr
 195 200 205
 50 Val Glu Pro His Lys Ile Arg Asp Ile Pro Val Thr Ile Met Asp Val
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 Phe Asp Gln Ser Ala Leu Ser Thr Glu Ala Lys Glu Glu Met Tyr Lys
 225 230 235 240
 55 Leu Tyr Pro Asn Ala Arg Arg Ala His Leu Lys Pro Gly Gly Asn Phe
 245 250 255
 60 Pro Tyr Leu Cys Arg Ser Ala Glu Val Asn Leu Tyr Val Gln Ile His
 260 265 270
 Leu Leu Gln Phe His Gly Thr Lys Tyr Ala Ala Ile Asp Pro Ser Met

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PCT/EP00/00506

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Patent claims

1. Nucleic acid, which includes
 - a) the nucleotide sequence shown in Fig.1 or a protein-coding segment thereof,
 - b) one of the sequence from a) within the context of the degeneration of the genetic code corresponding nucleotide sequence,
 - c) one with the sequences from a) and/or b) under stringent conditions hybridizing nucleotide sequence, except for the EST sequences:

AA165403, AA455594, AA314472, N34087, AA452340, AA182700, N41615, AA470049, AI751597, AA463289, AA132459, W31487, R56355, H58271, H16122, W77956, AA193332, AA323923, AA370209, AA296758, W72757, AA093971, AA385544, AA386175, AA165402, AW085713, H42806, AA093977, AI161152, AA370011, AI671702, R71215, AA885343, T79297, AI814869, R81567, AI082713, N29615, AW087726, AW075710, AI952608, AI818073, AI784445, AI432812, AI375568, AI372904, AI364106, AI143379, AA993074, AA953985, AA862385, AA761084, AA576229, AA569223, AA463198, AA452117, AA416877, AA074872, W16851, W04568, N40176, AW068354, AA857004, H58663, H15819, AW264944, AI923965, AI692214, AI475321, AI435987, AA961068, AA206059, AI469161, T84789, AA507257, AA707515, AA132458, AA179262, T79211, W31505, N25699, T99574, T99363, AI751598, AA713668, T91119, AW105515, AA370208, AI422128, R81568, AI038899, AI971847, AI540650, AI826106, AA885960, R56263, AA825431, T99147, D31503 and AF049564,or
 - d) a complementary sequence to the sequences of a) and/or b).
2. Nucleic acid according to claim 1, which includes a protein-coding segment comprising of preferably at least 30 nucleotides of the nucleotide sequence shown in Fig. 1.
3. Nucleic acid, which shows a homology of more than 65% with the nucleotide sequence according to claim 1 or a segment thereof.

4. Modified nucleic acid or nucleic acid analogue, which includes a nucleotide sequence according to one of the claims 1 to 3.
5. Recombinant vector, which includes at least one copy of a nucleic acid according to one of the claims 1 to 3 or a section thereof.
6. Recombinant vector according to claim 5, which enables the expression of the nucleic acid in a suitable host cell.
7. With a nucleic acid according to one of the claims 1 to 3 or a vector according to claim 5 or 6 transformed cell, a corresponding non-human transgenic organism or animal models, which stably produce (knock-in) the product of the nucleic acid according to one of the claims 1 to 3 or whose corresponding natural gene was destroyed deliberately (knock-out).
8. Polypeptide or a salt thereof, which is coded by a nucleic acid according to one of the claims 1 to 3.
9. Polypeptide according to claim 8, which exhibits
 - a) the amino acid sequence shown in Fig. 2 or
 - b) a homology of more than 60% with the amino acid sequence shown in Fig. 2 or a salt thereof.
10. Fragment of the polypeptide according to claims 8 or 9 with at least 100 amino acids or salts thereof.
11. Modified polypeptide, which includes an amino acid sequence according to claims 8 or 9.
12. Methods for the synthesis of the polypeptide according to claim 8 or 9, which includes the cultivation of cells according to claim 7 as well as the isolation of the polypeptide according to claim 8 or 9.
13. Use of a polypeptide according to claim 8 or 9 or of fragments of this polypeptide as an immunogen for the production of antibodies.

14. Antibodies against a polypeptide according to claim 8 or 9.
15. Method for the identification of effectors of a protein according to claim 8 or 9,
5 with the help of which various potential effector substances can be tested on cells,
which express the protein.
16. Pharmaceutical composition, which includes as active component
a) a nucleic acid according to one of the claims 1 to 4,
10 b) a vector according to claim 5 or 6,
c) a cell according to claim 7,
d) a polypeptide according to claim 8, 9, 10 or 11,
e) an antibody according to claim 14
and which contains the pharmaceutically usual carrier, auxiliary and/or additive
15 substances.
17. Use of a composition according to claim 16 for diagnosis of diseases, which are
associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis
and/or tumor progression, or a predisposition to such diseases.
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18. Use of a pharmaceutical composition for diagnosis of diseases which are associated
with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or
tumor progression, or a predisposition to such diseases, which contains as an active
component
25 a) an EST sequence according to claim 1c,
b) a recombinant vector which includes at least one copy of the EST sequences
mentioned above,
c) a recombinant vector according to b) which enables the expression of the
nucleic acid in a suitable host cell,
30 d) a cell according to claim 7, whereas the nucleic acid consists of one of the EST
sequences mentioned above,
e) a polypeptide being coded by one of the EST sequences mentioned above or a
salt thereof or,

- f) a polypeptide according to e) which exhibits the amino acid sequence shown in Fig.2 or a homology of more than 60% with the amino acid sequence shown in Fig.2 or a salt thereof,
- g) a fragment of the polypeptide according to e) or f) with at least 100 amino acids or a salt thereof,
- h) a modified polypeptide which includes an amino acid sequence according to e) or f),
- i) an antibody against a polypeptide according to e) or f) and which contains pharmaceutically usual carrier, auxiliary and/or additive substances.
19. Use of a composition according to claim 16 for the therapy or prevention of diseases, which are associated with DNA repair defects, cell cycle disorders, cytopenia, tumor genesis and/or tumor progression.
20. Use of a pharmaceutical composition according to claim 18 for the therapy or prevention of diseases, which are associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression.
21. Use of a composition according to claim 16 for a gene therapy of diseases, which are associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression.
22. Use of a pharmaceutical composition according to claim 18 for gene therapy of diseases which are associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression.
23. Methods for diagnosing diseases, which are associated with DNA repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression or a predisposition to such diseases, during which a patient or a sample from the patient is brought in contact with a composition according to claim 16 and the nucleotide sequence and/or the expression of a nucleic acid according to claim 1 is determined.
24. Methods for the therapy or prevention of diseases, which are associated with DNA

repair defects, cell cycle disorders, cytopenia, tumorigenesis and/or tumor progression, during which a patient is administered a composition according to claim 16, which contains the active components in an amount effective against the disease.

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Summary

cDNA sequence of an interactor FANCIP1 of the Fanconi anaemia protein of complementation group A

- 5 The present invention relates to the cDNA of an interactor FANCIP1 of the Fanconi anaemia protein of the complementation group A (FAA) as well as the thereof coded protein. Further issues are the corresponding gene, antibodies against the protein, FANCIP1-transgenic organisms and cells as well as the use of FANCIP1 for effector screening and the pharmaceutical application of the nucleic acid, the proteins and the
- 10 antibodies.

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Fig. 1

AAATGTCAGGATTAACCTCCATTTTCAGCTAATCATGGGAGAGATTAAAGTCTCTCCTGATTA
TAACTGGTTTAGAGGTACAGTTCCCCTTAAAAAGATTATTGTGGATGATGATGACAGTAAGA
TATGGTCGCTCTATGACGCGGGCCCCCGAAGTATCAGGTGTCCTCTCATATTCCTGCCCCCT
GTCAGTGGAAGTGCAGATGTCTTTTTCCGGCAGATTTTGGCTCTGACTGGATGGGGTTACCG
GGTTATCGCTTTGCAGTATCCAGTTTATTGGGACCATCTCGAGTTCTGTGATGGATTTCAGAA
AACTTTTAGACCATTTACAATTGGATAAAGTTCATCTTTTTGGCGCTTCTTTGGGAGGCTTT
TTGGCCCAGAAATTTGCTGAATACACTCACAATCTCCTAGAGTCCATTCCCTAATCCTCTG
CAATTCCTTCAGTGACACCTCTATCTTCAACCAAAGTTGGACTGCAAACAGCTTTTGGCTGA
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TACCTGTAAGTATTATGGATGTGTTTGATCAGAGTGCCTTTCAACTGAAGCTAAAGAAGAA
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CCTGTGCAGAAGTGCAGAGGTCAATCTTTATGTACAGATACATTTGCTGCAATTCATGGAA
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GAAGTACTTTTGAAGACTCCCATTTTAAAGAACCGTGCAGATTTTGCTACCAAAGTCTTCAC
CACTGTGTTCTTAAGTGAATGTTAATTTCTGAGGTTTGGGACTTTGTGGTGGTTTTTTTTCTT
CTTTTCTTTTCCATTCTTCTTTCTTTCTTTTATGTTGTTTGCTGTAAATGCTGCACATCCA
GATTGCATATCAGGACATTGGTTATTTTATGCTTTCTTGGATATAACCATGATCAGAGTGCC
ATGGCCACTACCCCACTGTTTGCTCTCCTGCAAATCAACTGCTTTTAATTTACACTTAAACA
AATTGTTTTGAGTGTTAGCTACTGCCTTTCTAGATATTAGTCATTTGGAATAAAAATTCAAT
TTC

Fig. 2

Met Gly Glu Ile Lys Val Ser Pro Asp Tyr Asn Trp Phe Arg Gly
Thr Val Pro Leu Lys Lys Ile Ile Val Asp Asp Asp Asp Ser Lys
Ile Trp Ser Leu Tyr Asp Ala Gly Pro Arg Ser Ile Arg Cys Pro
Leu Ile Phe Leu Pro Pro Val Ser Gly Thr Ala Asp Val Phe Phe
Arg Gln Ile Leu Ala Leu Thr Gly Trp Gly Tyr Arg Val Ile Ala
Leu Gln Tyr Pro Val Tyr Trp Asp His Leu Glu Phe Cys Asp Gly
Phe Arg Lys Leu Leu Asp His Leu Gln Leu Asp Lys Val His Leu
Phe Gly Ala Ser Leu Gly Gly Phe Leu Ala Gln Lys Phe Ala Glu
Tyr Thr His Lys Ser Pro Arg Val His Ser Leu Ile Leu Cys Asn
Ser Phe Ser Asp Thr Ser Ile Phe Asn Gln Thr Trp Thr Ala Asn
Ser Phe Trp Leu Met Pro Ala Phe Met Leu Lys Lys Ile Val Leu
Gly Asn Phe Ser Ser Gly Pro Val Asp Pro Met Met Ala Asp Ala
Ile Asp Phe Met Val Asp Arg Leu Glu Ser Leu Gly Gln Ser Glu
Leu Ala Ser Arg Leu Thr Leu Asn Cys Gln Asn Ser Tyr Val Glu
Pro His Lys Ile Arg Asp Ile Pro Val Thr Ile Met Asp Val Phe
Asp Gln Ser Ala Leu Ser Thr Glu Ala Lys Glu Glu Met Tyr Lys
Leu Tyr Pro Asn Ala Arg Arg Ala His Leu Lys Pro Gly Gly Asn
Phe Pro Tyr Leu Cys Arg Ser Ala Glu Val Asn Leu Tyr Val Gln
Ile His Leu Leu Gln Phe His Gly Thr Lys Tyr Ala Ala Ile Asp
Pro Ser Met Val Ser Ala Glu Glu Leu Glu Val Gln Lys Gly Ser
Leu Gly Ile Ser Gln Glu Glu Gln End

Fig. 3

Bco I: 5'-ACCAGCCTCTTGCTGAGTGGAGATG-3'

Bco II: 5'-GACAAGCCGACAACCTTGATTGGAG-3'

Fig. 4

FANCIP1-SP1: 5'-GGGGGCAGGAATATGAGAGG-3'

FANCIP1-SP2: 5'-TTTAAGGGGAAGTGTACCTC-3'



PATENT

ATTORNEY DOCKET NO: 50125/026001

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled cDNA SEQUENCE OF AN INTERACTOR FANCI1 OF THE FANCONI ANAEMIA PROTEIN OF COMPLEMENTATION GROUP A, the specification of which

☐ is attached hereto.

☒ was filed on August 2, 2001 as Application Serial No. 09/890,689
and was amended on _____

☐ was described and claimed in PCT International Application No. _____
filed on _____ and as amended under PCT Article 19 on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, § 1.56.

FOREIGN PRIORITY RIGHTS: I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Serial Number	Filing Date	Priority Claimed?
PCT	PCT/EP00/00506	January 24, 2000	Yes
Germany	DE 19904650.6	February 5, 1999	Yes

PROVISIONAL PRIORITY RIGHTS: I hereby claim priority benefits under Title 35, United States Code, § 119(e) and § 120 of any United States provisional patent application(s) listed below filed by an inventor or inventors on the same subject matter as the present application and having a filing date before that of the application(s) of which priority is claimed:

Serial Number	Filing Date	Status

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NON-PROVISIONAL PRIORITY RIGHTS: I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

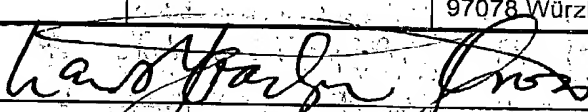
Serial Number	Filing Date	Status

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Paul T. Clark, Reg. No. 30,162, Karen L. Elbing, Ph.D. Reg. No. 35,238, Kristina Bieker-Brady, Ph.D. Reg. No. 39,109, Susan M. Michaud, Ph.D. Reg. No. 42,885, James D. DeCamp, Ph.D., Reg. No. 43,580, Sean J. Edman, Reg. No. 42,506, Timothy J. Douros, Reg. No. 41,716.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

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S. 5



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